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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	25

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/120,030	Applicant(s) Goldstein et al.
	Examiner Michael Borin	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 19, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4, 5, 28, 32, 35, and 41-60* is/are pending in the application.

4a) Of the above, claim(s) *28 and 35* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4, 5, 32, and 41-60* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Claims

1. Claims 33,34,36-39 are canceled. Claims 56-60 are added. Claims 4,5, 28,32,35, 41-60 are pending.

2. In regard to claims drawn to pharmaceutical composition, examiner erroneously indicated that claim reading on pharmaceutical composition is claim 32, instead of claims 28,35. Examiner apologizes for the inadvertent error, and inclusion of claims 28,35 in the rejections of claims drawn to methods of use. Claims 28,35 are withdrawn from consideration for the reasons set forth for claim 32 in the previous Office action. As for the traverse of the restriction requirement, Examiner maintains that the composition of claims 28,35 can be used in a materially different processes such as treating staphylococcal infection with lysostaphin administered via non-systemic routes (e.g., topical). The intended use recited now in the claim does not distinguish it from any other composition comprising recombinant lysostaphin. Further, the dosage limitations of the method claims require different searches for the two Groups. The restriction requirement is still deemed proper and is therefore made FINAL. Claims 28,35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected groups. Cancellation of claims 28,35 is requested.

Applicants arguments with respect to rejection made under 35 U.S.C. 103 have been considered but are deemed moot in view of the new grounds of rejection. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

3. Claims 4,5,32,41-60 are rejected are rejected under 35 U.S.C. 103(a) as obvious over Zygmunt, and Goldberg and Stark, and further in view of Oldham.

The instant claims are drawn to method of treating staphylococcal infection comprising systemic administration of a recombinantly produced lysostaphin analogue, wherein the lysostaphin analogue is administered with multiple doses per day of not more than 50 mg/kg.

Zygmunt

Zygmunt et al is a general reference reviewing properties of lysostaphin, its *in vitro* and *in vivo* applications, and various ways of administration. The reference teaches that lysostaphin is effective against a wide variety of staphylococcal infection, and is more potent than penicillins. The reference describes treatment of staphylococcal infections in various organs, such as kidney, heart valve (pages 319-

325). The dosage of lysostaphin varies in the range of 0.5 to 50 mg/kg (p. 320, Table 4). The ways of administration are intravenous, intraperitoneal, topical, intranasal (pages 319-324). Combined therapy with other antimicrobials, such as methicillin, augments effect of lysostaphin (p. 322). The reference also teaches pharmaceutical compositions comprising lysostaphin.

The reference does not teach multiple administrations of lysostaphin.

Goldberg (Antimicrobial Agents and Chemotherapy, p. 45-53, 1967).

Goldberg teaches treatment of staphylococcal infection in dogs with lysostaphin used intravenously at dosages 5-50 mg/kg. The administration was done multiple times, at intervals 1 to 24h. Treatment courses consisted of 1 to 23 injections over periods of 5h to 6.5 days. Lysostaphin treatment resulted in decrease of infection in lung,liver,spleen,kidney, and aortic and mitral valves. Heart valves were the most easily sterilized tissue. Adverse reactions to lysostaphin were not observed. See abstract ands Table 1.

In view of teaching of Goldberg, it would be obvious that lysostaphin cen be used either in singular or multiple administrations.

Zygmunt and Goldberg references do not teach administration of lysostaphin to humans.

Stark (N.Engl. J. Med, 291, 239-240, 1974; see specification, p. 3, lines 21-25).

Stark et al describes systemic administration of lysostaphin to a man suffering from staphylococcal pneumonia resulting from terminal unresponsive leukemia. The reference demonstrates that parenteral systemic administration of lysostaphin reduces bacteremia caused by strain of S. *Aureus* which proved to be resistant to methicillin, vancomycin and cephalothin. Single treatment with 500 mg of lysostaphin rapidly cleared microorganisms from pustule sites. The treatment removed staphylococci from blood, lungs, or abscess site.

Therefore, the prior art teaches that lysostaphin is effective both *in vitro*, in animal studies, and in humans. In regard to multiple administration to humans, as Goldberg teaches that lysostaphin is effective in animal studies when taken either in a single dose or repetitively, it would be obvious to select an appropriate regime of administration in humans as well. In regard to the particular dosage ranges, first, Goldberg teaches dosage range that overlaps with the claimed dosage ranges.

Second, if there are any differences between dosage ranges as claimed and that of the prior art, the differences would be appear minor in nature. Absent some teaching to the contrary, determination of particular ranges employed is within the skill of the ordinary worker as a part of the process of normal optimization.

The primary references do not teach recombinant lysostaphin or use thereof. It is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification). Oldham reference is used to demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product.

Oldham

Oldham et al teaches that lysostaphin can be produced recombinantly and demonstrates that recombinant lysostaphin, at low concentration of 5 μg/ml, is effective against *S. Aureus* in mammary tissue. See abstract. Note that administration to mammary tissue reads on the instantly claimed systemic administration, as the latter encompasses direct delivery to organs through injection (see specification, page 6, lines 31-32)

It would have been obvious to one skilled in the art at the time the invention was made to be motivated to use recombinant lysostaphin instead of the natural lysostaphin used in the primary references (e.g., in the systemic treatment described by Stark et al. Or Goldberg et al.), because it is easier to produce a recombinant analog of a natural product and because Oldham demonstrated that recombinant lysostaphin has high antimicrobial activity, similar to the natural product. Further, there is no evidence that lysostaphin produced recombinantly (i.e., natural lysostaphin recreated recombinantly) is any different from natural lysostaphin.

Further, in regard to lysostaphin analogs and use thereof, it is well known in the pharmaceutical art to develop and use new, improved analogs of known pharmaceuticals. As mechanism of action of lysostaphin is the lysis of the membrane wall of staphylococci, it would be obvious to develop and use new, more potent analogs of this well known antibiotic. Specification, p. 1, lines 26-34, is cited to exemplify lysostaphin analogs known in the prior art.

In regard to various locations of treatment, as Zygmunt teaches that lysostaphin is effective against more than 300 staphylococcus species and suggests its wide use at various locations, and as Stark suggests use of lysostaphin for treatment of human staphylococcal infections in lung, liver, brain, endocardium, and bone, it would have

been obvious to an artisan to apply this versatile antimicrobial at the sites which require antimicrobial treatment with the expectation, in the absence of evidence to the contrary, that such treatment will be successful.

4. Claims 32,42,43,46,4750,51,54,55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zygmunt, and Goldberg and Stark, and Oldham as applied above, and further in view of Dixon.

The instant claims are drawn to combination therapy of lysostaphin and another antimicrobial, in particular rifamycin or a glycopeptide. The primary references do not teach combined use of lysostaphin and rifamycin or a glycopeptide. However, Zygmunt teaches that lysostaphin is effective against staphylococcal infection only for limited time, and it is preferable to follow lysostaphin with another antibiotic. Dixon et al. teach that it is preferable to use lysostaphin in combination with other antimicrobials because a single dose usage of lysostaphin reduces dangers of hypersensitivity reaction. See p. 63, first paragraph. Because combination therapies for treatment of staphylococcal infection are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the probability that staphylococcal infection is minimized, it would be *prima facie* obvious to one of ordinary skills in the art at the time the invention was made to be motivated to use the

lysostaphin not only as a sole active pharmaceutical agent, but also in combination with other commonly used antimicrobials, such as rifamycin or glycopeptides.

Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 4,5,32,41-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims as amended recite administration multiple doses of lysostaphin per day, each dose of not more than 50 mg/kg. There is only one description in the specification of administering of the dosage of ≤50mg/kg (p. 4, line 10) but it does not include description of multiple administration per day of said dosage. Further, there is no description of administration of multiple doses of ≤50mg/kg lysostaphin per day to humans; all examples present in the specification are for animals.

Specification

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). There is no description of the dosage ranges recited in claims 52-55.

Conclusion.

7. No claims are allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL BORIN, PH.D
PRIMARY EXAMINER